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Electron Microscopic Study on Pathogenesis of Cerebral Edema in the White Matter

by

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INTRODUCTION

The increase in volume of the brain has been studied in various cerebral diseases for a long time. REICHARDT[21)22)] employed physical measurements to determine the increase of brain volume which had previously been called hypertrophy of the brain. His method entailed a comparison of the total intracranial volume with the brain volume. At the same time, two pathological entities were made on swollen brains, based on autopsy cases; one was called brain swelling, the other was designated as brain edema. The brain swelling (Hirnschwellung oder Hirnquellung) was characterized by a dry cut surface and the brain edema (Hirnödem) by an oozing of pinkish fluid from a cut surface [21)22)31)32)].

Later on, PERRET and KERNOHAN[20)] advanced their own idea on pathogenesis of increased brain bulk. Their opinion was that a clear distinction of brain swelling and brain edema was not possibly made on most of neurosurgical cases and that brain edema was rather considered as a late stage of severe brain swelling. EVANS and SCHEINKER[6)] tried to make a distinction between post-traumatic brain swelling and cerebral edema. However, they concluded that cerebral swelling generally preceded cerebral edema and was characterized by tumefaction of the axis cylinder, the myelin sheath, and the glial cells.

The discrepancy in pathological interpretation of brain swelling seems to be partly due to the methods employed in its investigation, and partly to the extremely complicated pathophysiological mechanisms behind it. All of methods so far available, light microscopy and chemical assay, seem to be strongly limited for solution of this problem : light microscopy, because of its inherent limitation of resolution, fails to reveal the changes manifest in the intracellular compartment ; chemical assay reveals only the total chemical changes present in the brain tissue, or samples thereof, but fails to define the exact localization of cellular or subcellular alterations. Electron microscopy, on the other hand, permits the study of the intracytoplasmic components of the neural, glial, and endothelial cells.

This paper was in part presented before 86th Annual Meeting of The American Neurological Association in Atlantic City, June 1961[7)]

The studies of cerebral swelling employing the electron microscope have thus far been made on swelling by intravenous injection of distilled water[15], by poisoning[30], by trauma[10][14], and by cold injury to the cortex[29]. All of these studies were limited to the examination of cerebral cortex. Brain swelling produced experimentally by such as those mentioned above, seems to bear little similarity in mechanism to the clinically observed brain swelling. Therefore, the production of brain swelling should be constant in mechanism, reproducible in various laboratories, and simulate as cosely as possible the mechanism active in causing cerebral swelling in the human. From this comprehensive standpoint, we applied, as one of the most ideal in experimental production of brain swelling, the epidural compression method[11][12]. The morphological changes of the cortex in brain swelling produced by the same method, have already been discussed in previous paper[12]. However, since the most obvious alterations in brain swelling are present in the white matter, the emphasis of this particular study has been placed on the alterations of white matter.

MATERIALS AND METHODS

The material for this study comprised 18 cats. The cats were anesthetized by giving nembutal intraperitoneally. The scalp was then shaved and a semicircular skin flap was turned over the left hemicranium. A small trephine opening was made. A small rubber balloon, to which a polyethylene catheter had been attached, was carefully inserted into the extradural space without epidural bleeding, and the bone button was replaced. The skin was closed with silk. Thereafter, the balloon was inflated very slowly and with great care by injecting sterile water through the polyethylene catheter. The volume of inflation differed from animals to animals, averaging 2.0ml. The exact end-point of inflation was extremely difficult to determine. We constantly observed that the maximum inflation tolerated by the cat, was indicated by the onset of mydriasis in the ipsilateral pupil. This end-point seems to be different from that observed in animals without anesthesia[12]. The polyethylene catheter was then sealed, and the inflated balloon was left in situ for 48 hours.

The specimens for light and electron microscopy were taken 0, 12, 18, 24 and 48 hours after removal of balloon from the swollen hemisphere of three cats in each group. Two per cent solution of osmium tetroxide, buffered with veronal acetate, was administered in the white matter and then in the lateral ventricle. The blackened brain tissue was selected as specimens for electron microscopy*.

The specimens were left in the fixative for one hour, then washed in distilled water, dehydrated by passing them through graded alcohol solutions, and finally embedded in Vestopal W[3]. The ultrathin sections were cut with PORTER-BLUM ultramicrotome, and stained with 2 per cent solution of uranyl acetate. They were examined with RCA EMU 3B electron microscope.

In a few animals, the specimens were taken with a sharp razor from the white

*After this experiment had been accomplished, Palay et al.[19] developed the perfusion method with osmium tetroxide solution for fixation of nervous system. The resulting pictures with our method seem to be as satiafactory as theirs.

matter right beneath the compression site as soon as both carotid arteries were cut, and were compared with those obtained by the former method. If the observation with electron microscope was selected to avoid the edge of the individual small specimens, the former method generally resulted in a more satisfactory preservation of the individual cells and their topographical correlation.

OBSERVATIONS

(1) Normal white matter of cat

(a) Blood vessel

The blood vessels are generally much sparser in distribution in the white matter than in the gray matter. Above all, the small blood vessels in the white matter give us a striking attention in their fine structure. There are two morphological patterns in regard to the existence of perivascular space, if the diameter of capillary in the white matter is less than 7μ as light microscopy has indicated. One of them (Fig. 1) reveals the perivascular space outside the endothelial lining. Collagen fibrils are present in the perivascular space. However, it is about 4μ in diameter and possesses in its wall 4 endothelial cells and 4 pericytes. Smooth muscle cell cannot be evident in the wall. On the other hand, some small blood vessel in the white matter, even much larger in diameter, possesses no perivascular space (Fig. 4). Furthermore, the former vessel is observed rather more frequently in electron microscopy than the latter. The fact that some of small blood vessels less than 6μ in diameter show a perivascular space in the white matter, may need a careful consideration in the classification of blood vessel, because the similar perivascular space has never been observed in the same-sized blood vessel in the gray matter[5)8)12)13)16)]. In brain swelling examined here, however, there are no significant differences in morphological changes of endothelial cells and of surrounding glial cells between the small blood vessels without and with the perivascular space. These observation may strongly suggest that the classification of capillary in the white matter must be based not only on its size and cellular constitution but also on its topographical correlation to the surrounding glial cells.

The arrangement and structural characteristics of endothelial cells are essentially similar in both types of blood vessels. The vessel lumen of both types is completely surrounded by elongated endothelial cells. No fenestration nor pores are evident in the endothelial sheet. The cell membrane of the endothelial cell is seen to be composed of triple-layered structure, namely unit membrane[23)24)25)], (Fig. 2) when sectioned in the perpendicular direction. Mitochondria and rough surfaced endoplasmic reticulum are seen to be sparsely distributed throughout the endothelial cytoplasm, except for perikaryon. Vesicles lined with triple-layered membrane, similar in structure to the cell membrane, are evident in few numbers in the endothelial cell. Some of them are connected with the cell membrane of the endothelial cell. In the vessel without perivascular space, only basement membrane is present between the endothelial sheet and the perivascular astrocytes In the vessel with perivascular space, on the contrary, two separate basement membranes, endothelial and astrocytic, are lined respectively close to the cell membrane of endothelial cells and perivascular astrocytes.

(b) Glial cells and extracellular space in the white matter

The morphological characteristics of astrocytes and oligodendrocytes in the white matter were described in detail in another paper[28]. The white matter is morphologically composed of a complicatedly interwoven meshwork of myelinated or unmyelinated fibers, oligodendrocytes, astrocytes, and their processes. They are tightly packed against each other, and the extracellular space intervening between the cellular components is measured 200A wide on the average. It is noticeable, however, that the tiny extracellular space, formed by three ovoid-shaped myelinated fibers, is triangular in shape and somewhat wider than the usual extracellular space between two glial cell processes (Fig. 5). This triangular extracellular space is lined with the intraperiod dense line visible on the surface of adjacent myelin sheaths.

The small blood vessels are directly or indirectly, depending upon the absence or the existence of perivascular space, completely surrounded by the processes of astrocytes, varying in size and shape. The extracellular space here between the perivascular astrocytes averages 200A in width similar to that in most area of the white matter. Moreover, electron dense materials are evident in few of extracellular space between two astrocytes in the vicinity of blood vessel (Fig. 3). An electron dense line, visible in the extracellular space, seems to be formed by fusion of peripheral leaflets of unit membrane of adjacent astrocyte cell membranes. A similar structure is seen in the terminal bars of the endothelial cell (Fig. 2).

(2) Pathological changes of white matter in brain swelling

Two stages, early and late, could be reasonably classified according to the difference of pathological changes in swollen brain tissue. The early stage of swelling in the white matter may be ranged 0 to 18 hours following the removal of balloon, whereas the late stage may be 24 hours and thereafter.

(a) Early stage of changes in the white matter (Fig. 6)

Many small vesicles are present in the cytoplasm of endothelial cells in early stage. The vesicles are bordered by the same triple-layered membrane as the endothelial cell membrane. Many vesicles are seen to accumulate on the luminal and the extravascular surfaces of endothelial cytoplasm. The presence of cell membrane invagination, associated with vesicles in the endothelial cell, is highly suggestive of pinocytosis[1)17)18)]. The mitochondria in the endothelial cell are very often swollen and show watery matrix. Few cristae are confined at the inner surface membrane of mitochondria. There is no evidence of any widening of the space between endothelial cells. The vesicles, similar in size and shape to those in the endothelial cell, are present in the cytoplasm of pericyte. It is extremely difficult to determine whether the perivascular space is distended or not, because of the variation in size of perivascular space even in the normal white matter. Vesicles, tiny particles, and mitochondria seem to be more concentrated in the perivascular astrocyte. The similar changes were observed in the perivascular astrocytes of gray matter in brain swelling[12)] The perivascular astrocytes are almost always increased in size and become watery in appearance.

Although the extracellular space, particularly in the vicinity of the blood vessel, is occasionally distended, the most portion of white matter maintains the normal width of

extracellular space. The swelling occurs exclusively in the cytoplasm of glial cells in the early stage.

(b) Late stage of changes in the white matter

Some of endothelial cells become swollen and watery in appearance. Many vesicles, rather large in size, are evident throughout the cytoplasm of endothelial cell. The rough surfaced endoplasmic reticulum is also distended. It may be suggested that pinched-off vesicles, representing pinocytic activity in the endothelial cell, are more numerous and larger as compared with those in the normal endothelial cytoplasm. Most of mitochondria are swollen on the one hand and some become electron dense in ground substance on the other. The mitochondria, changed into either morphology, still retain few cristae in their matrix. Dense bodies with homogeneous structure and one limiting membrane, are increased in number in the endothelial cell. Even in the later stage, there is no widening of the space between the endothelial cells. Electron dense materials are still present here. Macrophages are evident in the perivascular space of some small blood vessels. Few of them contain engulfed myelin debris and large dense bodies in their cytoplasm.

The perivascular astrocytes are swollen to a maximum degree and seem to show discontinuity of their cell membrane (Figs. 7 & 8). The mitochondria in astrocyte are swollen, and their cristae disappear often in a limited portion. Another characteristic change in astrocyte is increase of dense bodies, averaging 0.4μ in diameter, which consists of uniformly distributed dense matrix and one limiting membrane. Some of dense bodies show granular and vesicular profiles in matrix. There is no similarity in structure between mitochondria and dense bodies. It is noticeable in the perivascular astrocytes that numerous mitochondria and dense bodies are arranged between the glial fibrils as if they were associated with each other in cell functioning.

Some oligodendrocytes are swollen in cytoplasm and therefore the individual cytoplasmic organelles are distributed in a scattered fashion. Mitochondria and endoplasmic reticulum in oligodendrocyte are both considerably swollen (Fig. 9).

It is especially noteworthy in late stage of changes that the extracellular space is strikingly distended all over the white matter (Figs. 7, 8 & 9). Nerve fibers and glial cell processes are separated from each other to induce an extensive distension of extracellular space and therefore the cell membranes of individual cellular components make a boundary of this space. The distended extracellular space is too large in extent and strikingly irregular in shape to regard as the enlarged cytoplasm. One of the most reliable criteria to conclude as the distension of extracellular space is that any limiting or cell membranes can be never noticeable around this space and that there is no evidence of presence of cytoplasmic organelles in this extended space. Tiny particles in this space are possibly plasma protein derived from the blood stream (Figs. 8 & 9). It seems quite important in general that one cellular layer of perivascular astrocytes is almost always strongly attached to the astrocytic basement membrane and that there is no great widening of the extracellular space between the perivascular astrocytes in most cases.

DISCUSSION

It has been clearly shown that the perivascular space was never seen around the

capillary in the cerebral cortex[5)8)12)16)]. However, the electron microscopic observation of capillary has been so far limited to the cerebral cortex. Some of small blood vessels in the white matter, in spite of less than 6μ in diameter, show a narrow perivascular space containing collagen fibrils and occasional fibrocytes. This morphological characteristics have been observed only in venules or metarterioles in the gray matter. It may be possibly considered that osmium tetroxide makes the blood vessel contracted in fixation. However, this effect is in common with the blood vessel in both of gray and white matters. According to the conventional classification of capillary in the brain tissue, the capillary in the white matter could be defined as the small blood vessel without perivascular space, and the small blood vessel with perivascular space may be grouped into venule or metarteriole, based upon its cellular component of the vessel wall[5)8)12)16)].

On the whole, the capillary grouped here seems to be limited in number in the white matter as compared with that in the gray matter. The small blood vessel with perivascular space, venule or metarteriole, is encountered in electron microscopy in similar or a little more occurrence than the capillary. It means that the capillary portion seems too confined in extent to cover all of turnover event of metabolites through the blood vessels in the white matter. In addition, the morphological changes in brain swelling are similar in the endothelial and the perivascular glial cell of both types of blood vessels. These observations may strongly suggest that at least the venules are also possibly turnover site of metabolites in the white matter. If the morphological characteristic of blood-brain barrier is absence of perivascular space around the blood vessels, the distinguishing presence of this small blood vessels with perivascular space may become one explanation to much more vulnerability to the changes in brain swelling in the white matter than in the gray matter. However, the blood-brain barrier exists even in the white matter. This fact may urge us to reconsider the morphological characteristic of blood-brain barrier.

In the white matter, nerve fibers, whether myelinated or unmyelinated, oligodendrocytes, astrocytes, or their cytoplasmic processes are packed together compactly, and subsequently the extracellular space is only 150 to 200A wide as in the gray matter[5)8)13)26)], except for the triangular space formed by three myelinated fibers. Accordingly, metabolic exchange between blood stream and nervous tissue—especially nerve fibers—in the white matter may be carried out through the glial cell; possibly the astrocyte, since astrocytes are commonly located between blood vessels and nerve fibers, as in the gray matter.

In brain swelling, the presence of numerous vesicles is noticed in the cytoplasm of endothelial cell. The morphological characteristic of the vesicle is highly suggestive of pinocytosis, initially found in the endothelial cell by PALADE[17)18)] and BENNETT[1)]. These vesicles are seen to accumulate on the luminal surface of endothelial cytoplasm, and then on the extravascular surface facing the endothelial basement membrane. Consequently, the entry of intravascular fluid into the endothelial cell may be carried out by the process of pinocytosis. This passing mechanism through the endothelial cell was clarified with ferritin particles administered intravenously[9)27)]. The basement membrane is somewhat swollen, presumably because of arrival of large amount of fluid. However, any vesicle formation cannot be observed here. We believe that the passage across the basement membrane of fluid do not involve biological process from the morphological point of view.

It has been reported that accumulation of vesicles, particles, and mitochondria was noted in the perivascular astrocytes, exclusively in the portion abutting upon the basement membrane, in the swollen cerebral cortex[12]. The changes observed in the perivascular astrocyte of the swollen white matter seem to have some similarity. It may be considered, here, that the fluid, transported through the basement membrane, is picked up by the perivascular astrocytes, possibly again through the mechanism of pinocytosis, and transported through the perivascular astrocyte in vesicles. Mitochondria and glial fibrils in the perivascular astrocyte also might have an unknown contribution to the transportation of fluid. Dense bodies, possibly lysosomes[2)4)], in the endothelial cell and the astrocyte may do something for fluid transportation. The tracer experiment with ferritin particles strongly back up these possibilities[9)27)]. It is entirely unknown, however, into what subcellular compartment of glial cytoplasm the fluid, encircled by vesicular membrane, is finally discharged. The continuous and excessive passage of fluid into the perivascular astrocytes distends these cytoplasm markedly. The similar transportation process of fluid may occur successively in all glial cytoplasms in the white matter and in consequence, the total white matter is increased in volume as a result of intracellular enlargement in early stage of swelling in the white matter.

When this transportation process becomes excessive in amount in late stage, the glial cells are distended to a maximum degree. At the same time, the extracellular space become distended here and there. One layer of perivascular astrocytes almost always maintains their original site and surrounds completely the blood vessle, showing no great distension of extracellular space between them in most cases. It may be greatly indicated that the attachment between the astrocytic basement membrane and the perivascular astrocyte cell membrane is strikingly strong. It seems to be assumed unreasonably, therefore, that the strikingly extensive distension of extracellular space in the white matter is due to the excessive fluid transportation through the extracellular space between the perivascular astrocytes. The most possible mechanism is that excessive entry of fluid into the perivascular astrocytes may disturb their cellular function, including its active transport mechanism and subsequently that the transported fluid intolerable in amount to the cellular function of astrocyte, may not be picked up here and begin to leak between the cellular components, thereby separating the cellular components from one another. Even if the discontinuity of cell membrane of astrocyte is artificial, it may strongly suggest the possibilty supposed above, because the discontinuity of cell membrane is not shown in endothelial cells and macrophages but only in glial cells in the same sectioned specimens. The astrocyte, which possibly participates in active transport of fluid in the brain, is rather strikingly limited in number in the white matter because of innumerable nerve fibers. This fact might be responsible for more vulnerability to brain swelling in the white matter.

The pathological changes of brain swelling in the cerebral cortex were observed previously with electron microscope, employing the same extradural compression method[12]. The increase in volume of the cerebral cortex is mainly due to the enlargement of individual glial cells, whereas in the white mater the distension of both the intra- and extracellular spaces makes a great contribution to the enlargement of its bulk. In other words, the

mechanism underlying in brain swelling might be somewhat different between the cerebral cortex and the white matter. Therefore, one should use different nomenculatures to call the alterations of the cerebral cortex and the white matter. The pathological changes in the cerebral cortex should be named brain swelling, whereas those in the white matter should be designated as brain edema, as REICHARDT[21)22)] and ZÜLCH[31)32)] differentiated both pathological changes. However, the extracellular space between the perivascular astrocytes seems to make no fluid pathway significant for the extensive distension of extracellular space in the white matter. The finding of brain swelling produced by our method may indicate further that brain swelling precedes cerebral edema in the white matter, as PERRET and KERNOHAN[20)], and EVANS and SCHEINKER[6)] mentioned previously on the basis of their light microscopy.

The detailed study of morphological changes of axon, myelin sheath, and glial cells was described in another paper[27)28)].

SUMMARY

The capillary in the white matter may have no perivascular space as that in the cerebral cortex does not, but is strikingly limited in number on the whole. However, it is noted here that another blood vessel, less than 6 or 7μ in diameter, possesses a narrow perivascular space where collagen fibrils are present and moreover that this blood vessel is observed in similar or a little more frequency than the capillary in the white matter. Both types of blood vessels show almost similar morphological changes in brain swelling. The morphological representation of blood-brain barrier is reconsidered from this standpoint.

In brain swelling, the fluid is passed from the blood vessel lumen into the endothelial cell possibly by the process of pinocytosis. The fluid, arrived in the basement membrane, may be picked up into the perivascular astrocyte mostly by the similar pinocytic mechanism and transported in the similar fashion into one astrocyte after another.

In early stage, astrocyte is swollen considerably, possibly because of large amount of fluid transported from the blood stream. Therefore, the increased volume of the white matter in this stage is mainly due to the intracellular swelling. In late stage of brain swelling, the astrocyte is strikingly swollen to a maximum degree, and at the same time the extracellular space is remarkably distended. Therefore, the increase in volume of the white matter in brain swelling is due to both intra-and extracellular distension. The possible mechanism is discussed on the extensive distension of extracellular space.

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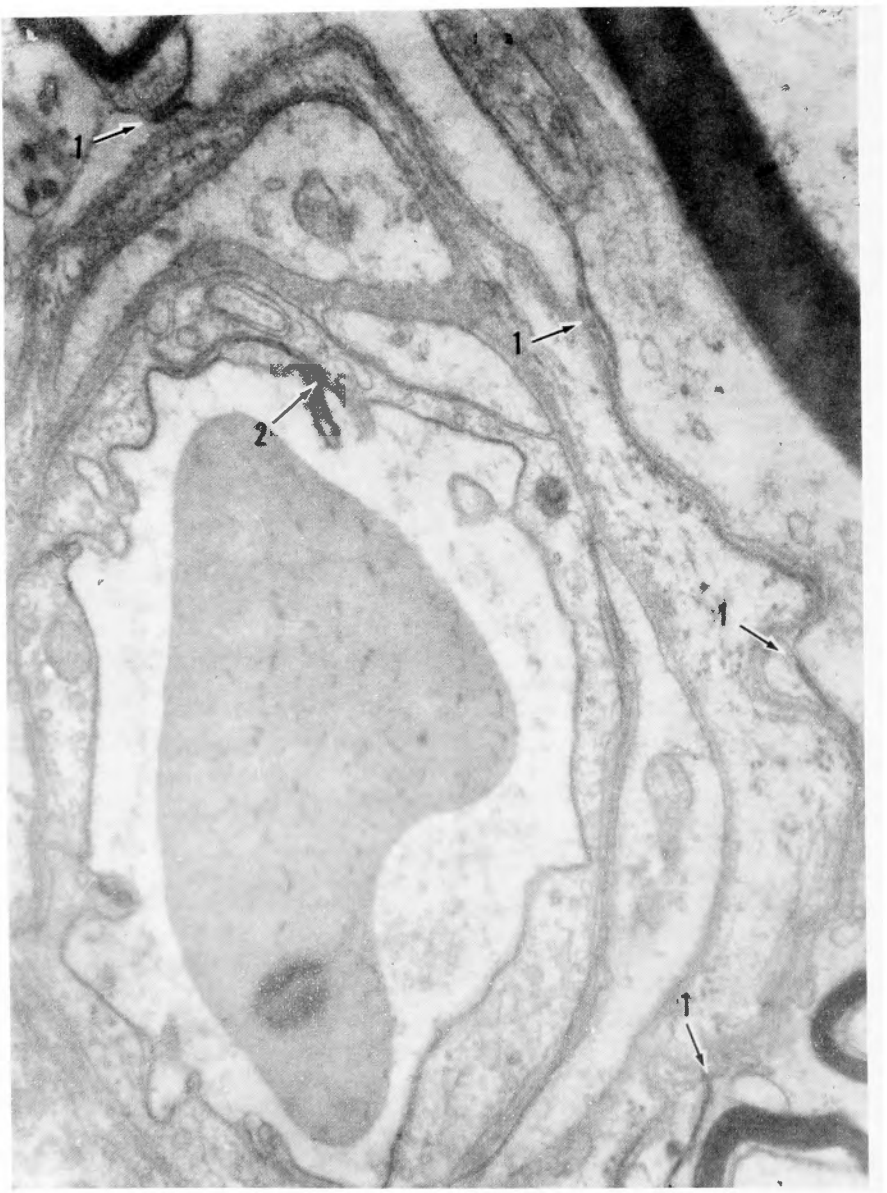

Fig. 1. This small blood vessel, about 4μ in diameter, is composed of 1 endothelial cells and the same number of pericytes. A perivascular space, where collagen fibrils are sectioned transversely or longitudinally, is surrounded by two basement membranes. They are abutting respectively on the cell membranes of endothelial cells or pericytes and perivascular astrocytes. Four extracellular spaces (arrow 1) between the adjacent astrocytes are electron dense in appearance which is similar in structure to the boundary between two endothelial cells (arrow 2).

Mag. ×32,000

Figs. 2 and 3. Higher powered pictures of the extracellular space between endothelial cells (Fig. 2) or astrocytes (Fig. 3.) Vesicles in the endothelial cell show unit membrane in appearance. The peripheral surfaces of unit membrane structure in endothelial cell membrane are united to form a dense line in the extracellular space. A dense line, which is probably formed by the similar process, is visible between the adjacent perivascular astrocytes.
Mag. ×120,000 in both figures

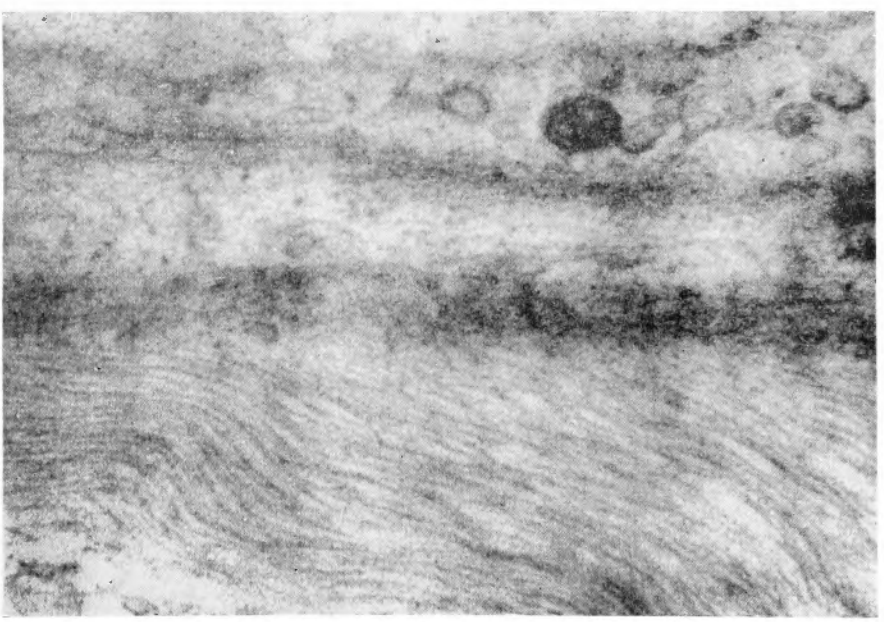

Fig. 4. A portion of capillary in the white matter is surrounded by endothelial cell and pericyte. Many glial fibrils, mostly sectioned longitudinally, are evident in a perivascular astrocyte. Some gliofilaments reveal a suggestive structure of cylindrical density. There is no perivascular space between the capillary wall and the astrocyte.
Mag. ×110,000

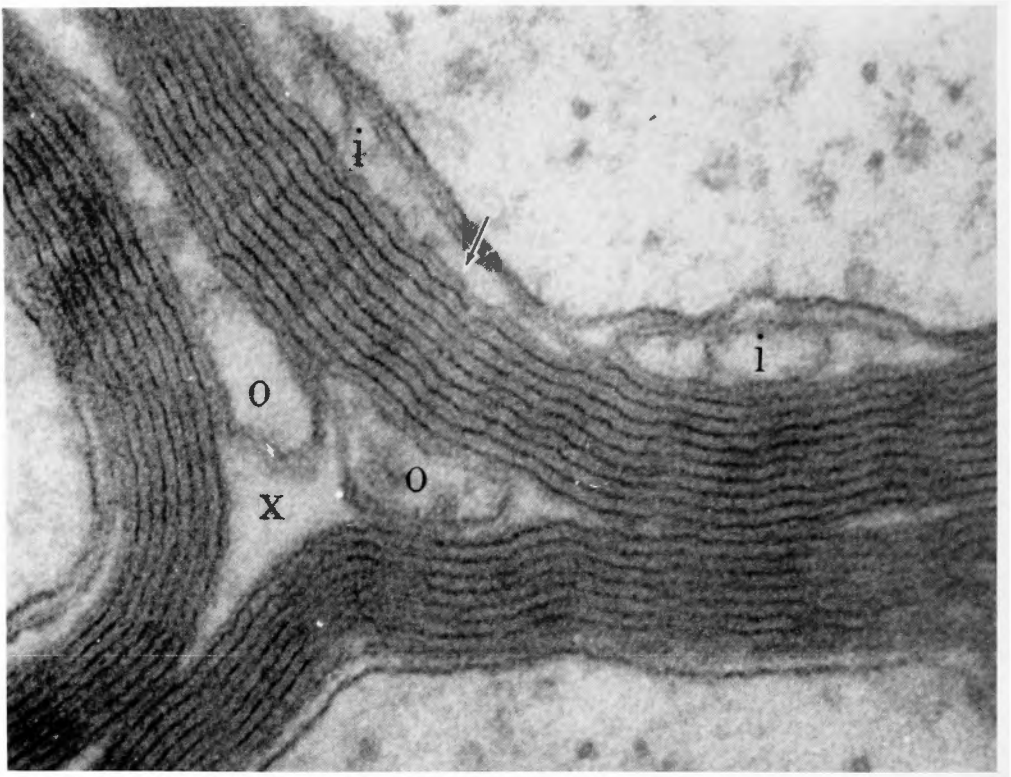

Fig. 5

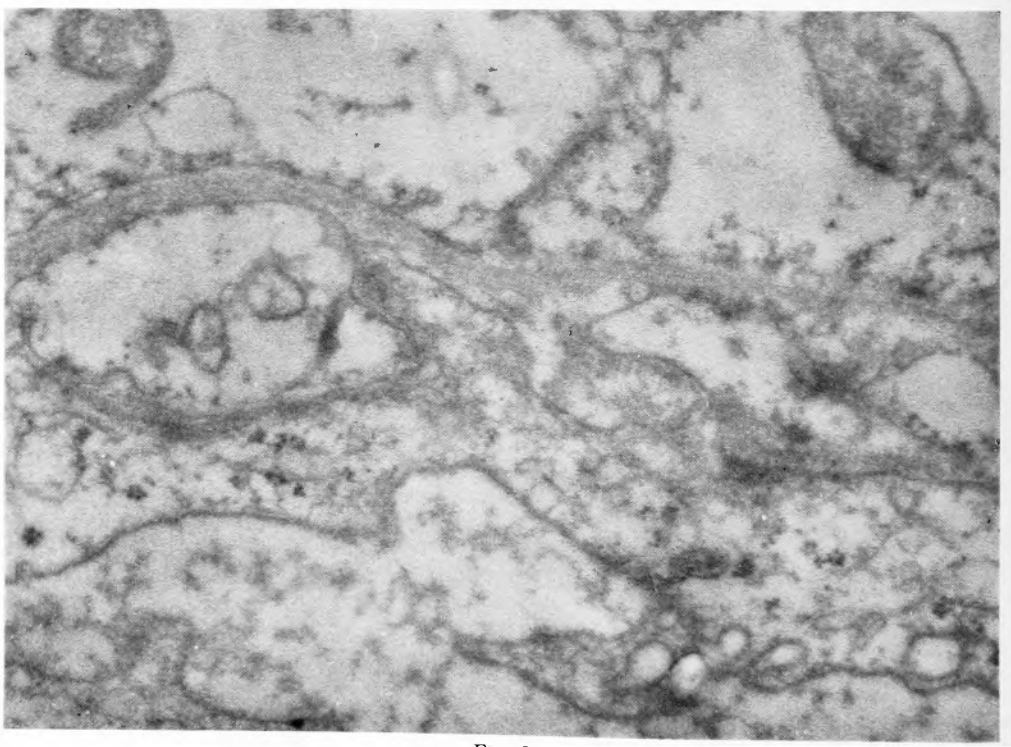

Fig. 6

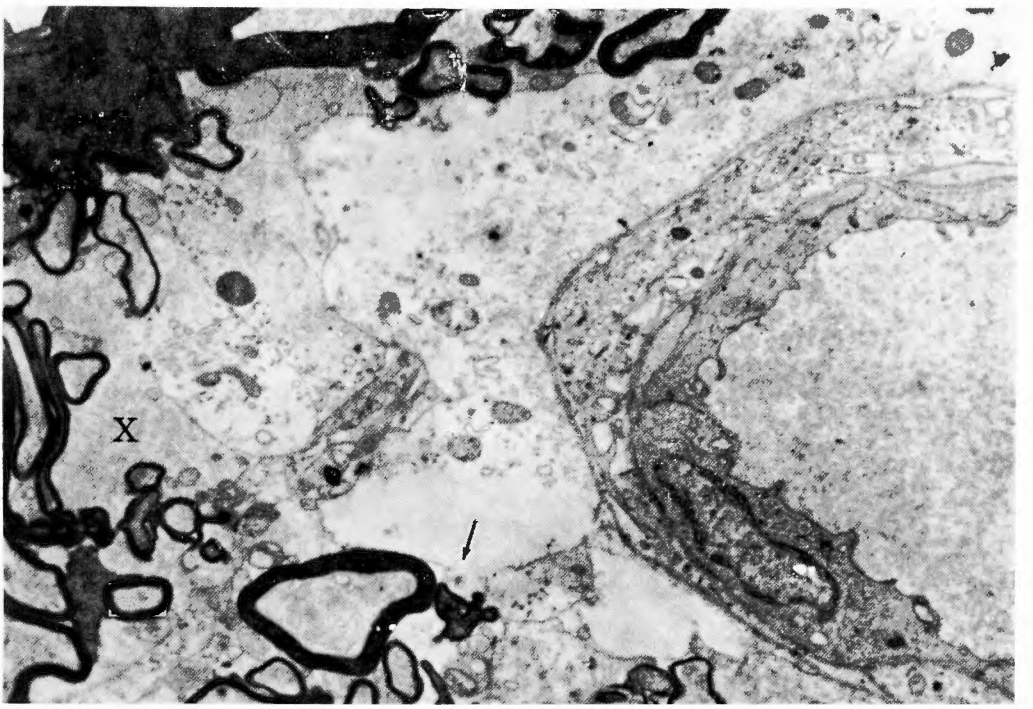

Fig. 7

Fig. 8

Fig. 9

Fig. 5. A rather wider extracellular space (x), triangular in shape, is formed by three adjacent myelin sheaths and surrounded by the intraperiod dense lines. The cell membrane of inner (i) and outer (o) loops is composed of unit membrane. Its peripheral leaflet formes the intraperiod dense line, and its cytoplasmic leaflet is fused to make the major dense line. A less dense structure is radially passed throughout the entire width of myelin sheath, particularly in the vicinity of outer loop (arrow). Mag. ×180,000

Fig. 6. A blood vessel immediately after the removal of balloon. The endothelial cells and the perivascular astrocytes are both swollen in appearance. Several vesicles are seen associated with the endothelial cell membrane in the lower right. Many of small vesicles and particles are similarly associated with the cell membrane of perivascular astrocyte abutting on the basement membrane. Mag. ×40,000

Fig. 7. A blood vessel and perivascular astrocytes at 24 hours after the removal of balloon. All of perivascular astrocytes are swollen and discontinuity of cell membrane (arrow) is visible in the astrocytes. Some of mito-

chondria are swollen. Many flocculent materials are evident in the distended extracellular space (x).
Mag. ×14,000

Fig. 8. The perivascular astrocyte shows discontinuous cell membrane (x). An extensively distended extracellular space (x) is present among the glial cells and nerve fibers. The picture is taken from the specimen at 24 hours after the removal of balloon. Mag. ×25,000

Fig. 9. An extensive evagination of nuclear membrane is shown in an oligodendrocyte at 24 hours after the removal of balloon. Small vesicles are seen in this large nuclear membrane gap. Mitochondria and endoplasmic reticulum are both evidently swollen. Mag. ×18,000

和文抄録

脳白質浮腫発生機序に関する電子顕微鏡学的観察

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要　　約

白質の毛細血管は灰白質同様血管周囲腔は存在しないが，その分布は極めて少ない．しかし，白質の血管で注目される事は，直径が6乃至7μ以下で，血管壁の構成は毛細血管と同じでありながら，膠原原繊維の存在する血管周囲腔がある事であり，且つ毛細血管と同様乃至は少し多い頻度で分布している．脳腫脹時には，この両者の血管の形態学的変化に有意の差は認められない．以上の点より，この血管周囲腔を有する細血管部も物質交換の場と考えられるが，この点より従来の血液脳関門の形態学的特徴に一考を要する必要がある．

脳腫脹時には，pinocytosisにより血液内液性成分が内皮細胞層を通過して基底膜に達し，そこから同様の過程をへて血管周囲の星状膠細胞から隣接せる他の星状膠細胞に次々に伝わつて行くものと考えられる．

脳腫脹初期には，血液由来の液性成分のため，主として星状膠細胞が著明に膨大し，細胞内腫脹による白質容積の増大を来すが，末期には，これに加えて細胞外腔の著しい増大がみられ，従つて細胞内及び細胞外腔の増大によつて白質組織全体が膨大するものである．細胞外腔増加の形態的変化を電子顕微鏡学的所見より考察を試みた．